

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF ELECTION
(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

United States Patent and Trademark
Office
(Box PCT)
Washington D.C. 20231
United States of America

in its capacity as elected Office

| | |
|--|--|
| Date of mailing: 23 May 1995 (23.05.95) | |
| International application No.: PCT/US94/10308 | Applicant's or agent's file reference: P50186-2 |
| International filing date: 07 September 1994 (07.09.94) | Priority date: 07 September 1993 (07.09.93) |
| Applicant: HOLMES, Stephen, Dudley et al | |

1. The designated Office is hereby notified of its election made:

in the demand filed with the International Preliminary Examining Authority on:

31 March 1995 (31.03.95)

in a notice effecting later election filed with the International Bureau on:

2. The election was

was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

| | |
|---|--|
| The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35 | Authorized officer: J. D. Hawkins Telephone No.: (41-22) 730.91.11 |
|---|--|

PATENT COOPERATION TREATY

PCT

NOTIFICATION CONCERNING
DOCUMENT TRANSMITTED

From the INTERNATIONAL BUREAU

To:

United States Patent and Trademark
Office
(Box PCT)
Washington D.C. 20231
United States of America

Date of mailing (day/month/year)
31 October 1995 (31.10.95)

in its capacity as elected Office

International application No.
PCT/US94/10308

International filing date (day/month/year)
07 September 1994 (07.09.94)

Applicant

SMITHKLINE BEECHAM CORPORATION et al

The International Bureau transmits herewith the following documents and number thereof:

copy of the international preliminary examination report (Article 36(3)(a))

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Authorized officer

K. Andreasson

Facsimile No.: (41-22) 740.14.35

Telephone No.: (41-22) 730.91.11

PATENT COOPERATION TREATY

26 OCT 1995

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

| | | |
|--|---|---|
| Applicant's or agent's file reference PS0186-2 | FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416) | |
| International application No. PCT/US94/10308 | International filing date (day/month/year) 07 SEPTEMBER 1994 | Priority date (day/month/year) 07 SEPTEMBER 1993 |
| International Patent Classification (IPC) or national classification and IPC Please See Supplemental Sheet. | | |
| Applicant SMITHKLINE BEECHAM CORPORATION | | |

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

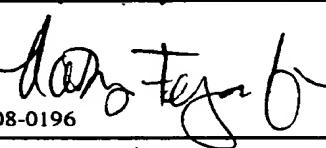
2. This REPORT consists of a total of 14 sheets.

This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority. (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 0 sheets.

3. This report contains indications relating to the following items:

- I Basis of the report
- II Priority
- III Non-establishment of report with regard to novelty, inventive step or industrial applicability
- IV Lack of unity of invention
- V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI Certain documents cited
- VII Certain defects in the international application
- VIII Certain observations on the international application

| | |
|--|--|
| Date of submission of the demand 31 MARCH 1995 | Date of completion of this report 21 SEPTEMBER 1995 |
| Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230 | Authorized officer PAULA HUTZELL Telephone No. (703) 308-0196  |

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US94/10308

I. Basis of the report

1. This report has been drawn on the basis of (*Substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments*):

the international application as originally filed.

the description, pages 1-74, as originally filed.

pages NONE, filed with the demand.

pages NONE, filed with the letter of _____.

pages , filed with the letter of _____.

the claims, Nos. 1-38, as originally filed.

Nos. NONE, as amended under Article 19.

Nos. NONE, filed with the demand.

Nos. NONE, filed with the letter of _____.

Nos. , filed with the letter of _____.

the drawings, sheets/fig 1-11, as originally filed.

sheets/fig NONE, filed with the demand.

sheets/fig NONE, filed with the letter of _____.

sheets/fig , filed with the letter of _____.

2. The amendments have resulted in the cancellation of:

the description, pages NONE.

the claims, Nos. NONE.

the drawings, sheets/fig NONE.

3. This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box Additional observations below (Rule 70.2(c)).

4. Additional observations, if necessary:

NONE

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US94/10308

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**1. STATEMENT**

| | | |
|-------------------------------|---------------------------|-----|
| Novelty (N) | Claims <u>1-31, 34-38</u> | YES |
| | Claims <u>32, 33</u> | NO |
| Inventive Step (IS) | Claims <u>NONE</u> | YES |
| | Claims <u>1-38</u> | NO |
| Industrial Applicability (IA) | Claims <u>1-38</u> | YES |
| | Claims <u>NONE</u> | NO |

2. CITATIONS AND EXPLANATIONS

Claim 32 lacks novelty under PCT Article 33(2) as being anticipated by Ramanathan et al. who teach monoclonal antibodies that bind to human IL-4 and neutralize biological activity.

Claims 32-33 lack novelty under PCT Article 33(2) as being anticipated by Kaneko et al. who teach neutralizing monoclonal antibodies specific for human IL-4 which have a binding affinity of equal to or less than $2 \times 10^{10} M$.

Claims 1-30 and 33-38 lack an inventive step under PCT Article 33(3) as being obvious over Queen et al. in view of Abrams et al. or Kaneko et al., or Ramanathan et al. or Chretien et al.

Queen et al. teach that methods for cloning the genes encoding antibodies, methods for the production of nucleic acid constructs encoding CDR-grafted antibodies, and methods for the production of host cells expressing said constructs were well known in the art at the time of applicant's invention.

Ramanathan et al., Kaneko et al., Abrams et al. and Chretien et al. each teach methods for producing monoclonal antibodies that bind to and inhibit human IL-4 and teach that anti-IL-4 monoclonal antibodies are potentially useful for in vivo human therapy and for diagnostic immunoassays. (Continued on Supplemental Sheet.)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US94/10308

Supplemental Box

(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

~~Sheet 10~~**CLASSIFICATION:**

The International Patent Classification (IPC) and/or the National classification are as listed below:
IPC(6): C07K 16/24, 16/46, 17/02; C07H 15/12; G01N 33/53; C12P 21/08; C12N 5/10, 5/20, 15/13; A61K 39/395 and US Cl.: 530/387.3, 388.25, 391.1; 536/23.53; 435/7.1, 70.21, 172.2, 240.2, 240.27, 320.1; 424/133.1, 134.1, 145.1

V. 2. REASoNED STATEMENTS - CITATIONS AND EXPLANATIONS (Continued):

It would have been obvious to one of ordinary skill in the art at the time of applicant's invention to produce hybridomas secreting neutralizing anti-IL-4 monoclonal antibodies according to the methods taught by Ramanathan et al., Kaneko et al., Abrams et al. and Chretien et al. One would have expected to obtain cell lines producing antibodies with dissociation constants of 2×10^{-10} or less in view of the fact that antibodies having dissociation constants in this range were routinely isolated by standard hybridoma techniques. Having obtained hybridomas producing anti-IL4 neutralizing antibodies it would have been obvious to use the hybridomas as the starting materials in the methods taught by Queen in order to produce nucleic acid constructs encoding fusion proteins which are CDR-grafted antibodies. It would have been obvious to introduce the constructs so-obtained into suitable hosts for expression. One would have been motivated to produce the claimed inventions in view of the art-recognized advantages of humanized antibodies for *in vivo* therapeutic use and in view of the art-recognized potential usefulness of anti-IL4 monoclonal antibodies for *in vivo* human therapy. The claimed fusion proteins, nucleic acids, recombinant plasmids and hosts, antibodies and hybridomas and methods of producing and using antibodies do not appear to differ in any unobvious or unexpected manner from those that one of ordinary skill in the art would have expected to obtain in view of the cited references. It would have been obvious to use anti-IL4 antibodies in immunoassays in view of the combined teachings of the cited references.

Claim 31 lacks an inventive step under PCT Article 33(3) as being obvious over Abe et al. in view of Abrams et al. or Kaneko et al., or Ramanathan et al. or Chretien et al.

Abe et al. teach a method for the production of high affinity monoclonal antibodies. It would have been obvious to use a method such as that taught by Abe et al. in order to produce and select for high affinity antibodies having specificity for IL-4. One of ordinary skill would have been motivated to do so in order to obtain the art-recognized advantages of high-affinity antibodies in the analytical and therapeutic applications for which anti-IL4 antibodies were taught to be useful by Abrams et al., Kaneko et al., Ramanathan et al. and Chretien et al.

----- NEW CITATIONS -----
NONE



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

| | | | |
|--|--|--|---|
| (51) International Patent Classification ⁶ : C07K 16/24, 16/46, 17/02, C07H 15/12, G01N 33/53, C12P 21/08, C12N 5/10, 5/20, 15/13, A61K 39/395 | | A1 | (11) International Publication Number: WO 95/07301 (43) International Publication Date: 16 March 1995 (16.03.95) |
| (21) International Application Number: PCT/US94/10308 (22) International Filing Date: 7 September 1994 (07.09.94) (30) Priority Data: 08/117,366 7 September 1993 (07.09.93) US 08/136,783 14 October 1993 (14.10.93) US | | Road, Wayne, PA 19087 (US). SYLVESTER, Daniel, R. [US/US]; 42 Rossiter Avenue, Phoenixville, PA 19460 (US). | |
| (60) Parent Application or Grant (63) Related by Continuation US 08/136,783 (CIP) Filed on 14 October 1993 (14.10.93) | | (74) Agents: SUTTON, Jeffrey, A. et al.; SmithKline Beecham Corporation, Corporate Intellectual Property, UW2220, 709 Swedeland Road, P.O. Box 1539, King of Prussia, PA 19406-0939 (US). | |
| (71) Applicants (for all designated States except US): SMITHKLINE BEECHAM CORPORATION [US/US]; Corporate Intellectual Property, UW2220, 709 Swedeland Road, P.O. Box 1539, King of Prussia, PA 19406-0939 (US). SMITHKLINE BEECHAM PLC [GB/GB]; New Horizons Court, Brentford TW8 9BD (GB). | | (81) Designated States: AM, AU, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LV, MD, MG, MN, MW, NO, NZ, PL, RO, RU, SD, SI, SK, TJ, TT, UA, US, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CL CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD). | |
| (72) Inventors; and (75) Inventors/Applicants (for US only): HOLMES, Stephen, Dudley [GB/GB]; Yew Tree Bottom Road, Epsom, Surrey KT15 5XQ (GB). GROSS, Mitchell, Stuart [US/US]; 667 Pugh | | Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i> | |

(54) Title: RECOMBINANT IL4 ANTIBODIES USEFUL IN TREATMENT OF IL4 MEDIATED DISORDERS

(57) Abstract

Chimeric and humanized IL4 MAbs derived from high affinity MAbs, pharmaceutical compositions containing same, and methods of treatment are provided.

Serial No.: 08/612,929

Group Art Unit: 1806

| | <i>Col 1</i> | | <i>Col 2</i> | <i>Col 3</i> | <i>Other than a small entity</i> | |
|--|-------------------------------------|-------|---|------------------|----------------------------------|-------------------|
| | Claims Remaining After Amendment | | Highest Number Previously Paid For | Present Extra | Rate | Additional Fee |
| Total | 27 | Minus | 38 | 0 = 0 | 0 x 22 = | 0.00 |
| Indep | 12 | Minus | 13 | 0 = 0 | 0 x 82 = | 0.00 |
| [] First presentation of Multiple Dependent Claim | | | | | + 270 = | 0.00 |
| | | | | | Total | 0.00 |

The "Highest Number Previously Paid For" (Total or Independent) is the highest number found from the equivalent box in Col. 1 of a prior amendment or the number of claims originally filed.

[] No additional fee is required for the amendment(s).

[X] Charge \$950.00 to Deposit Account No. 19-2570. Two copies of this form are enclosed.

Please charge any additional fees under 37 CFR 1.16 or 1.17 which may be required by this paper, or credit any overpayment, to Deposit Account No. 19-2570. Also, should the Patent and Trademark Office determine that the fee calculated in the above extension petition is not deemed sufficient to have this response considered as being timely filed, this constitutes a petition for extension of time for the minimum period to effect timely filing, and the Commissioner is authorized to debit any necessary fee to said deposit account.

Respectfully submitted,

Alissa M. Eagle
Attorney for Applicants
Registration No. 37,126

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Facsimile (610) 270-5090

INTERNATIONAL SEARCH REPORT

Int'l application No.
PCT/US94/10308**A. CLASSIFICATION OF SUBJECT MATTER**

IPC(6) :Please See Extra Sheet.

US CL :Please See Extra Sheet.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 530/387.3, 388.25; 536/23.53; 435/7.1, 70.21, 172.2, 240.2, 240.27, 320.1; 424/133.1, 134.1, 145.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS, CAS ONLINE, BIOSIS, MEDLINE, SWISSPROT, GENESEQ 3

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|-----------|--|-----------------------|
| Y | WO, A, 90/07861 (QUEEN ET AL.) 26 JULY 1990, SEE ENTIRE DOCUMENT. | 1-29 |
| Y | US, A, 5,041,381 (ABRAMS ET AL.) 20 AUGUST 1991, SEE ENTIRE DOCUMENT. | 1-38 |
| X --- | JP, A, 91-187,395 (KANEKO ET AL.) 15 AUGUST 1991, SEE ENTIRE DOCUMENT. | 32, 33, 36-38 |
| Y | | ----- 1-31, 34, 35 |
| X --- | WO, A, 91/09059 (RAMANATHAN ET AL.) 27 JUNE 1991, SEE ENTIRE DOCUMENT. | 32 ----- |
| Y | | 1-31, 33-38 |

Further documents are listed in the continuation of Box C. See patent family annex.

| | | |
|---|-----|--|
| * Special categories of cited documents: | "T" | later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention |
| "A" document defining the general state of the art which is not considered to be of particular relevance | "X" | document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step |
| "E" earlier document published on or after the international filing date | "Y" | when the document is taken alone |
| "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) | "&" | document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art |
| "O" document referring to an oral disclosure, use, exhibition or other means | | document member of the same patent family |
| "P" document published prior to the international filing date but later than the priority date claimed | | |

Date of the actual completion of the international search Date of mailing of the international search report

09 DECEMBER 1994

09 JAN 1995

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231
Facsimile No. (703) 305-3230

Authorized officer

PAULA HUTZELL

Telephone No. (703) 308-0196

INTERNATIONAL SEARCH REPORT

Int'l application No.

PCT/US94/10308

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|-----------|---|-----------------------|
| Y | JOURNAL OF IMMUNOLOGICAL METHODS, VOLUME 117, ISSUED 1989, CHRETIEN ET AL., "DEVELOPMENT OF POLYCLONAL AND MONOCLONAL ANTIBODIES FOR IMMUNOASSAY AND NEUTRALIZATION OF HUMAN INTERLEUKIN-4", PAGES 67-81, SEE ENTIRE DOCUMENT. | 1-38 |
| Y | HYBRIDOMA, VOLUME 12, NUMBER 4, ISSUED AUGUST 1993, ABE ET AL., "NOVEL IMMUNIZATION PROTOCOL AND ELISA SCREENING METHODS USED TO OBTAIN AND CHARACTERIZE MONOCLONAL ANTIBODIES SPECIFIC FOR HUMAN LIGHT CHAIN VARIABLE-REGION SUBGROUPS", PAGES 475-483, SEE ENTIRE DOCUMENT. | 31, 32 |

INTERNATIONAL SEARCH REPORT

Int'l application No.
PCT/EP94/10308

A. CLASSIFICATION OF SUBJECT MATTER:

IPC (6):

C07K 16/24, 16/46, 17/02; C07H 15/12; G01N 33/53; C12P 21/08, C12N 5/10, 5/20, 15/13; A61K 39/395

A. CLASSIFICATION OF SUBJECT MATTER:

US CL :

530/387.3, 388.25, 391.1; 536/23.53; 435/7.1, 70.21, 172.2, 240.2, 240.27, 320.1; 424/133.1, 134.1, 145.1

| | |
|---|--|
| Applicant's or agent's file reference number P50186-2 | International Application No. PCT/US94/10308 |
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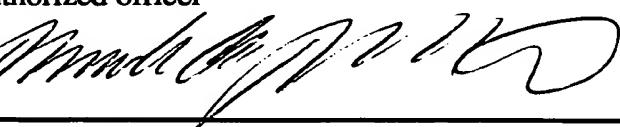
INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

| | |
|---|-------------------------------------|
| A. The indications made below relate to the microorganism referred to in the description on page 32, line 14. | |
| B. IDENTIFICATION OF DEPOSIT | |
| Name of depositary institution European Collection of Animal Cell Cultures (ECACC) | |
| Address of depositary institution (including postal code and country) Porton Down Salisbury Wiltshire, SP4 OJG United Kingdom | |
| Date of Deposit 06 October 1993 | Accession Number 93100620 |
| C. ADDITIONAL INDICATIONS (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/> | |
| In respect of those designations in which a European or Australian Patent is sought or in any other states having equivalent provisions, a sample of the deposited micro-organism will be made available until the publication of the mention of the grant of the patent or until the date on which the application has been refused or withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample. | |
| D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States) All | |
| E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable) | |
| The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications, e.g., "Accession Number of Deposit") | |

For receiving Office use only

For International Bureau use only

| | |
|---|--|
| <input checked="" type="checkbox"/> This sheet was received with the international application | <input type="checkbox"/> This sheet was received by the International Bureau on: |
| Authorized officer  | Authorized officer |